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Cancer with Phosphorus-31 Magnetic Resonance Spectroscopy

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13. ABSTRACT (Maximum 200 Words) The objective of the proposed research is to develop 1H-decoupled 31P magnetic resonance spectroscopy (MRS) techniques for measuring non-invasively the response of breast cancer to induction or preoperative chemotherapy. We hypothesize that the quantitative assessment of the effectiveness of a treatment using 31P MRS will be clinically feasible at 3.0T. Although the hardware modifications made to the MR scanner to enable 31P MRS were completed, and a breast RF coil was constructed and tested successfully, significant delays in the delivery of the scanner and in the manufacturer providing scanner software to properly operate at the phosphorus frequency resulted in poor progress. Patient scanning was not achieved. It is expected that some patients will be scanned in the near future using another source of funding in order to complete the goals of the study.				
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INTRODUCTION

Advances in the understanding of the biology of breast cancer are leading to the identification of novel therapeutic targets, the development of new cytotoxic agents and strategies for treatment of this disease. The identification of suitable early markers of tumor response to a specific chemotherapeutic agent will make it possible to customize an effective treatment for each patient, rejecting ineffective drugs early in treatment, and tailoring the regimens for effective agents for optimum response. Phosphorus-31 (^{31}P) magnetic resonance spectroscopy (MRS) can provide information non-invasively on alterations in tumor metabolism caused by chemotherapy in women with breast cancer. Thus, the objective of the proposed research is to develop ^1H -decoupled ^{31}P MRS techniques for measuring noninvasively the response of breast cancer to induction or preoperative chemotherapy. To validate our approach, we propose first, to perform measurements using appropriate standards and, second, a pilot study including women with breast cancer undergoing induction chemotherapy.

During the previous reporting period, the Siemens Trio 3.0 T clinical MR scanner, which was originally designed by the manufacturer to perform only proton MR imaging and spectroscopy, was modified electronically to permit operation at the phosphorus frequency for the purposes of this project. In the current period, the coil and scanner were tested for performance in both proton imaging and phosphorus spectroscopy. The manufacturer installed a multinuclear hardware upgrade to the scanner, which was intended to permit convenient operation at various nuclear frequencies including phosphorus, in addition to normal operation at the proton frequency. This upgrade was expected to make operation at both frequencies robust and routine, and was expected to enable the project to proceed to completion. However, the scanner software was not fully compatible with phosphorus operation, and much of this period was spent unsuccessfully in attempting to get the scanner to work properly at the phosphorus frequency, including multiple and continuing consultations with various Siemens engineers.

Since the stated goals of the project were not met by the end of this period, we have made arrangements to obtain additional (private) funding to continue with this project so that the essential goals of the proposed work can be eventually reached. We have been informed by Siemens that the software which will make operation at the phosphorus frequency work properly will be available in the summer of 2004, at which time the project is expected to continue.

BODY

The Siemens Trio 3 Tesla high field MR scanner located in the MGH NMR Center did not originally have a multinuclear capability, and therefore had to be modified to perform phosphorus-31 localized spectroscopy. In the previous period (please see previous report), we installed electronic modifications to the scanner such that our own front-end electronics was interposed between the RF coil and the scanner, enabling the scanner to work as normally at its proton frequency, while our modifications shifted the operating frequency to and from the phosphorus frequency. This proved to be a successful procedure, and images and spectra of ^1H and ^{31}P in phantoms were obtained with the breast RF coil produced during the current period.

During the current period, a modification to this scheme was made, with the assistance of Siemens engineers, to eliminate some of our external electronics by using the frequency conversion electronics of the scanner itself, making the switchover between ^1H and ^{31}P more

convenient. Rapidity in this changeover is essential when scanning patients. For ^{31}P operation we modified a spare transmitter board to allow us to introduce our own intermediate frequency and mix down to the 3 Tesla ^{31}P frequency of 49.9 MHz. The presence of ^1H bandpass filters in the RF transmission line between the coil plug socket in the patient bed and the final stage transmit/receive box of the Siemens scanner (TALES unit) also required that we connect directly to the TALES unit. Using this set-up ^1H images (Figure 1), ^{31}P images (Figure 2) and ^{31}P spectra (Figure 3) of a phosphoric acid phantom were acquired with the $^{31}\text{P}/^1\text{H}$ breast coil.

Figure 1 (left) shows a photograph of the breast coil as seen from the patient's point of view. The right panel in the figure shows the tuning circuitry in one half of the coil. The view is from the bottom of the coil. The proton coil is a loop on the outer side of the coil, and provides adequate uniformity and signal-to-noise ratio (SNR) for proton scout images. The phosphorus coil is a full Helmholtz design which uniformly covers the entire breast.

Figure 2 shows ^1H 2D spin echo images in two planes of a phantom (a bottle containing 85% phosphoric acid) test object. Good signal-to-noise ratio was obtained. The proton image spatial uniformity is not high because of the decision to optimize the coil receptivity for ^{31}P , which is much more critical in these experiments. This is explained in detail below.

Figure 3 shows spin echo images at the phosphorus frequency in three planes. These images demonstrate that the ^{31}P RF field uniformity is quite high.

Figure 4 shows the single pulse ^{31}P spectrum of the phantom. The signal-to-noise ratio (SNR) achieved in this phantom (16 M in phosphorus) is 3100:1 with 10 averages in an FID acquisition with $\text{TR} = 2$ s. When extrapolated to the *in vivo* situation ($\sim 1\text{--}5$ mM) this yields an anticipated signal to noise ratio roughly on the order of 1:1 in the same amount of time (20 s). With signal averaging for 20 min on a patient this should provide a factor of 7–8 in SNR. Other potential optimizations (pulse sequence optimization, decoupling and nuclear Overhauser enhancement, etc.) give confidence that adequate SNR will be achieved when patients are scanned.

Tumor spectroscopy requires that spectra be obtained from the tumor volume while rejecting signal from adjacent volumes. Figure 5 shows a selective (or single) volume spectroscopy (SVS) ^{31}P spectrum of the phantom acquired using the STEAM pulse sequence with this setup. The acquisition parameters were: voxel volume = 15 cm^3 , repetition time $\text{TR} = 1.18$ s, number of averages = 32, Lorentzian line broadening = 10 Hz. Again, the SNR of this spectrum indicates that patient spectroscopy will work as planned.

The breast coil was further characterized for ^1H RF field (and image) uniformity and for SAR (specific absorption rate), which is a measure of the RF dose to which the patient is subjected during scanning. Figure 6 shows a series of proton gradient echo images in which a large flip angle is used. This creates a fringe effect which helps to visualize the relative RF field intensity (as well as coil receptivity) spatial pattern; the more closely spaced the fringes, the stronger the RF field (and correspondingly, the higher the receptivity). The RF coil has been optimized for ^{31}P receptivity and spatial uniformity of response, whereas the proton channel of the coil is intended to be used only for simple imaging with sufficient performance to localize the tumor (higher performance MRI will already have been performed on each patient). Therefore it was decided that some compromise of the proton spatial uniformity could be tolerated so that the phosphorus channel could be fully optimized.

The specific absorption rate (SAR) is a measure of the amount of RF power absorbed by tissue as a result of the operation of the scanner, and must be kept with FDA specified limits such that the scanning procedure is considered a nonsignificant risk. The $^1\text{H}/^{31}\text{P}$ breast RF coil

was tested on the scanner at both operating frequencies using pulse sequences that typified the RF power dosing to be used on patients. A normal saline gel phantom filling one breast cavity of the coil was used to simulate the RF absorption characteristics of breast tissue. A Luxtron fiber optic temperature monitor was used to sample the temperature rise in four locations in the phantom for at least 20 minutes while the pulse sequences ran. It was found that for both the proton and phosphorus pulse sequences there was no significant temperature rise, indicating that there would be no risk of RF heating for these pulse sequences.

Proton decoupling is the process by which the protons are irradiated while phosphorus spectra are acquired, and has two potential advantages. First, it eliminates spin-spin coupling between protons and phosphorus, thereby narrowing and simplifying those phosphorus spectral lines which are subject to proton coupling. Second, it enables a magnetization transfer effect which increases the intensity of the phosphorus spectral lines, an effect known as the nuclear Overhauser enhancement (NOE). Both of these effects tend to increase the phosphorus SNR. The NOE depends on a number of factors such as the relaxation rates of the nuclei involved, and may or may not be fully effective for particular resonances. The maximum NOE for ^{31}P with ^1H couplings is about 2.2, which would be equivalent to a five-fold reduction in scanning time. We therefore undertook the construction of a decoupling channel for the scanner. The decoupler is driven by a logic device which produces a WALTZ-4 pattern of decoupling pulses (a particularly efficient decoupling mode which allows reduced SAR). The TTL pulses from the pattern generator control an RF gate fed by a frequency synthesizer at the proton frequency. The low level RF pulse output of this device is fed to an RF power amplifier and then to the coil. When the decoupler is operating only during the acquisition of the ^{31}P signal, spectral decoupling is achieved. When operated continuously at lower power (except at full power during ^{31}P signal acquisition) the NOE effect is also obtained.

Although the hardware for ^{31}P spectroscopy is now in place, continuing problems with the scanner operation at the ^{31}P frequency prevent using the scanner on patients. When operated in service mode (with safety monitoring off) the scanner, our preamplifier circuits and our RF coil work well. However, in normal operating mode the scanner software complains of RF faults and will not continue with the ^{31}P scan. However, these faults do not appear to actually exist, since the scanner works well in service mode, and all RF parameters are within appropriate limits. Service mode cannot be used for the research because the safety protections are not fully in place, and long term signal averaging does not function properly. We have worked with Siemens engineers on a continuing basis on this problem, and have not been able to solve it. The software currently installed on the scanner is not the full official release for multinuclear capability on this particular scanner model, and therefore operation at the ^{31}P frequency is technically not supported. We have been informed by Siemens that the software fully supporting ^{31}P operation will be available later this year.

We are therefore planning to carry through with this project insofar as possible, using private funding. It is expected that with the next software release the scanner will function properly, enabling some breast cancer patients to be studied with ^{31}P localized spectroscopy.

KEY RESEARCH ACCOMPLISHMENTS

- Construction and testing of the double tuned $^1\text{H} - ^{31}\text{P}$ RF coil
- Conversion of the MR scanner to acquire ^{31}P NMR spectra

- Obtaining proton and phosphorus MR images from the coil
- Testing of the signal-to-noise ratio and RF field uniformity of the coil at both operating frequencies
- Measurement of RF specific absorption rate (SAR) in a normal saline gel phantom
- Construction of proton decoupler

REPORTABLE OUTCOMES

Poster presentation, Era of Hope Department of Defense Breast Cancer Research Program Meeting, September 25–28, 2002, Orlando, FL.

CONCLUSIONS

Although the project was held up due to problems with the MR scanner software, the hardware components necessary for the research are in place and functioning. The final goal of scanning patients was not accomplished. However, once the next software release is installed enabling the scanner to perform ^{31}P in vivo spectroscopy, we plan to continue with the study by scanning several breast cancer patients. The value of this work is that it will eventually enable the use of ^{31}P MR spectroscopy in the management of breast cancer.

REFERENCES

n/a

PERSONS SUPPORTED BY THIS PROJECT

Leoncio Garrido, Ph.D., Christian T. Farrar, Ph.D., Jerome L. Ackerman, Ph.D.

APPENDICES

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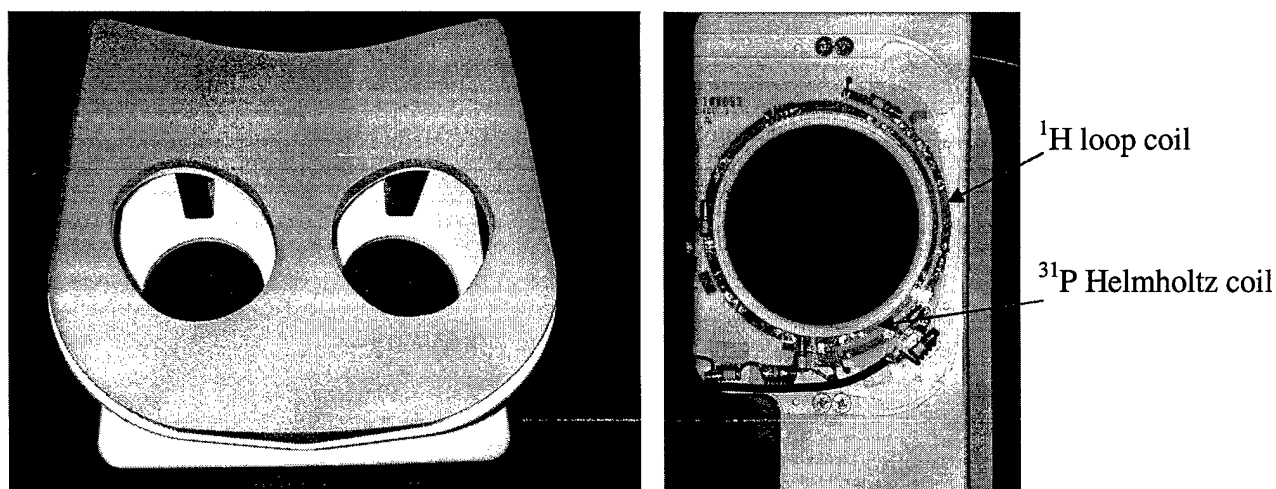


Figure 1. (Left) Photograph of the $^1\text{H} - ^{31}\text{P}$ double tuned breast coil as seen from the patient's view. (Right) View from the underside, cover removed, showing the separate ^1H and ^{31}P RF coils. The ^1H coil is a single lateral loop, providing adequate if nonuniform coverage of the breast for scout scans, while the ^{31}P coil is a Helmholtz design uniformly encompassing the entire breast.

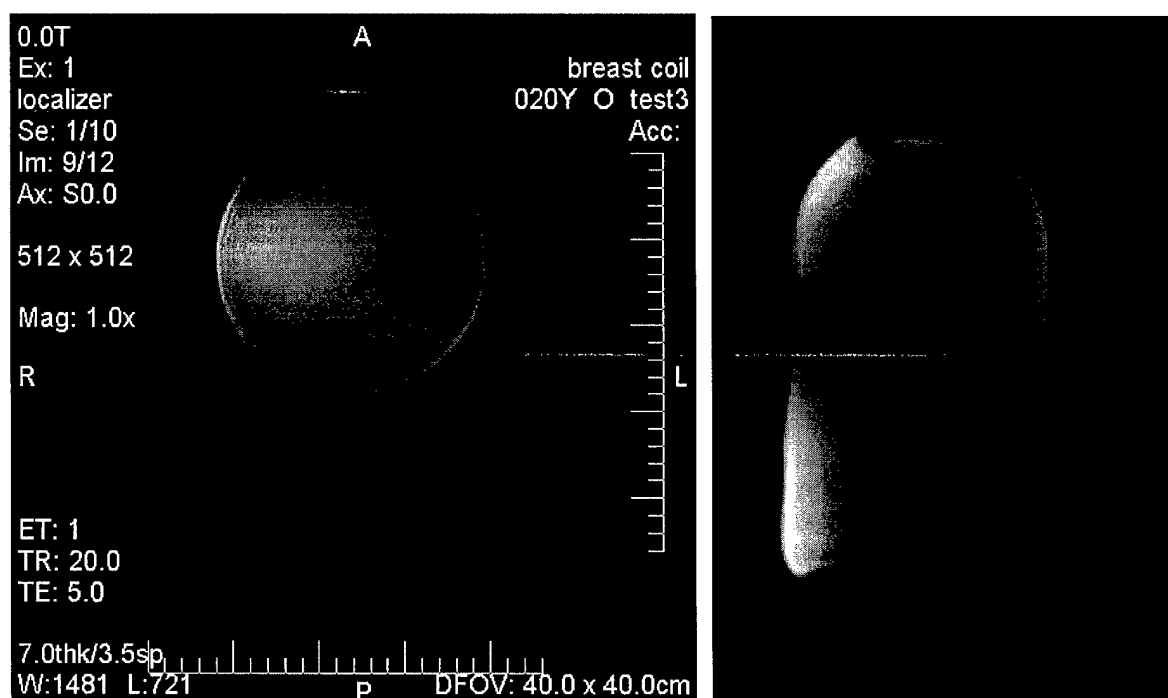


Figure 2. Axial (left) and coronal (right) proton spin echo images of the $^1\text{H}/^{31}\text{P}$ phosphoric acid phantom. The spatial uniformity is not high, but adequate for scout images.

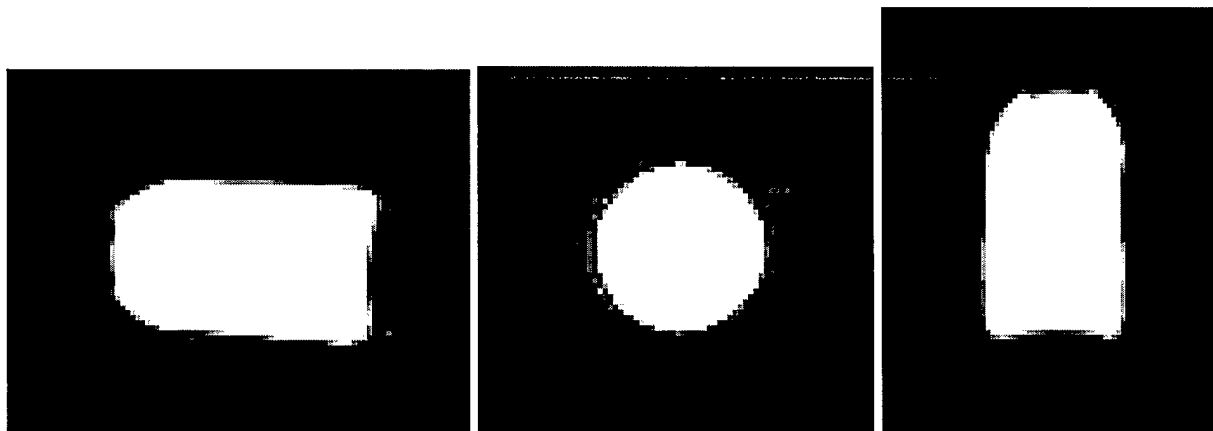


Figure 3. (Left to right) Sagittal, coronal, and axial ^{31}P images of the phosphoric acid phantom. The spatial uniformity of the RF field is quite good.

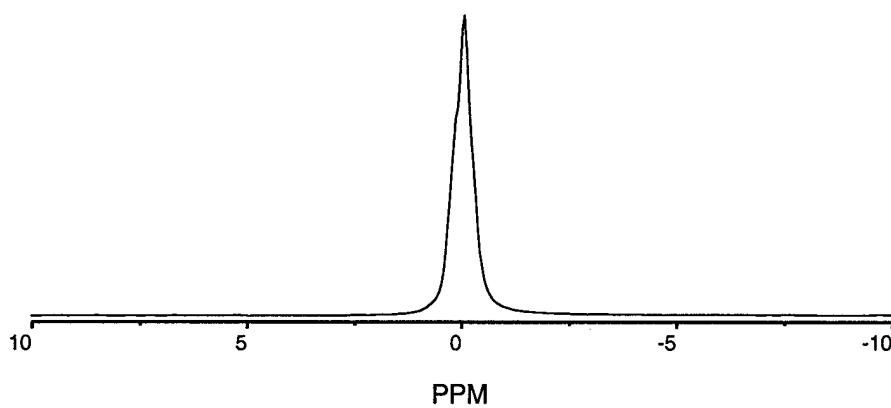


Figure 4. Single pulse ^{31}P spectrum of the phantom, yielding an excellent signal-to-noise ratio of 3100:1 with 10 averages.

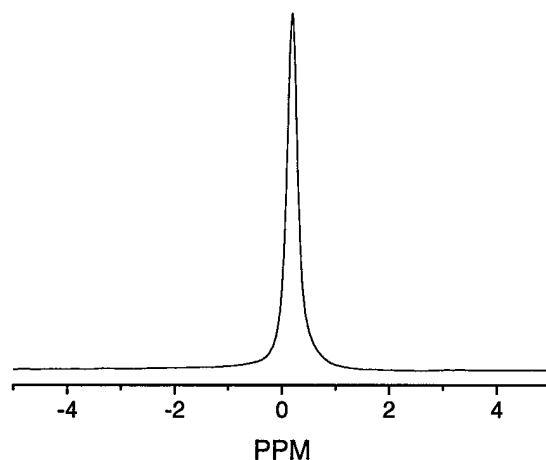


Figure 5. Selective volume spectroscopy of the phosphoric acid phantom acquired using the STEAM pulse sequence at 3 Tesla (49.9 MHz). Acquisition parameters: Voxel volume = 15cm^3 , repetition time $TR = 1.18\text{ s}$, number of averages $NA = 32$, linebroadening $LB = 10\text{ Hz}$.

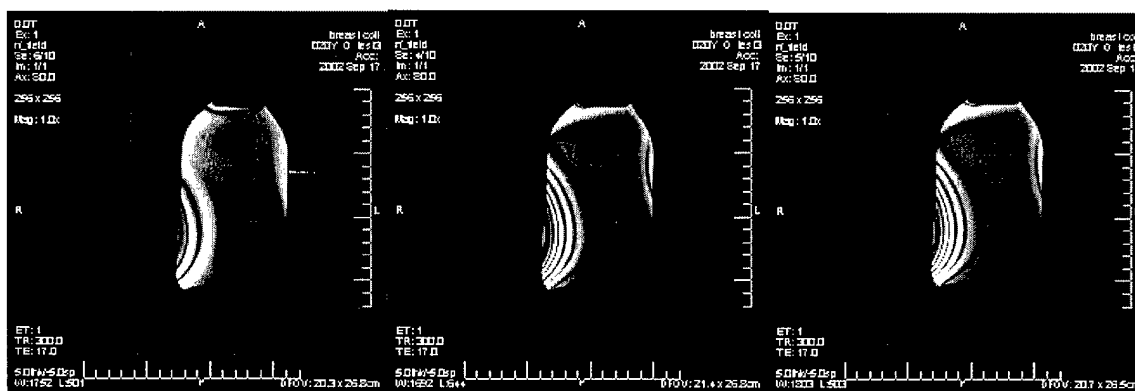


Figure 6. ^1H gradient images of the phantom with large flip angles to yield fringes (corresponding to successive 360° rotations of the magnetization) whose spacing is a measure of the RF field intensity (and by reciprocity the signal detection sensitivity); the closer the fringes, the higher is the RF field. The flip angles are 360° , 720° and 750° .